CHAVI RFA Question and Answer Document

QUESTION 1: On page 14 it says that "potential CHAVI investigators and their institutions other than the CHAVI Director and the Initial members of the scientific leadership group are not to be named in the application." On the other hand, a key component of the CHAVI is to write, in 50 pages, the research plan and the scientific plan upon which the grant will be judged. If the research plan is contingent on having vectors X, Y and Z available for development to solve the vector problem, can these sources be named and it documented that the vectors mentioned will be available? Otherwise if one writes, "we will develop vector X in the CHAVI", but show no source or no documentation of having it, then the review group will recognize this is a problem. This general concept applies to getting letters from computational biologists, structural biologists, etc. and others who will need to collaborate, join, be involved, etc. to give credibility to the research and strategic plans. Also, regarding the size of the scientific leadership group, the RFA mentions "to include the names of three to four initial members of the Scientific Leadership Group who will contribute to the planning, etc." Is the 3 to 4 membership of the SLG hard and fast? Can one go to 6?

ANSWER: We want you to demonstrate your understanding of the obstacles to HIV/AIDS vaccine development and vision for how to overcome them (in your SCIENTIFIC PLAN) and your capability to implement that vision in a new, innovative vaccine immunology center (in your STRATEGIC PLAN); these (and the Management & Operations Plan) are the crucial elements of the Application. Your concerns regarding the limitations on listing all of your potential collaborators in your application appears to be based on a misunderstanding of the RFA. With the CHAVI RFA we are looking for an applicant with the capability and vision to establish and run an extramural HIV Vaccine Immunology Center comparable to the Vaccine Research Center on the NIH campus led by Dr. Gary Nabel. This is more than an effort to get a single vaccine into a clinical trial (as DAIDS funds through its IPCAVD and HVDDT awards). It is also more than a "gigantic IPCAVD" designed to get several vaccines into clinical trials. We want the Center to break new ground by doing targeted basic research in vaccine discovery and design, rather than just drive some already existing vaccine candidates through product development into clinical trials. But we also want the Center to understand and have the ability to do product development because pure basic research in the absence of a product development/manufacturing orientation can lead down impractical avenues.

The research program should start by addressing scientific gaps as identified by the Global HIV Vaccine Enterprise as stated in the RFA under Objectives and Scope ["(a) the elucidation of early immunologic and virologic events after HIV-1 exposure/infection in humans, including studies of exposed, uninfected persons and of HIV-infected persons during the acute to early stage of disease and/or; (b) the elucidation of the correlates of immune protection in nonhuman primate models in which there was protection from acquisition of infection (e.g., postinoculation antiretroviral treatment to prevent establishment of persistent, productive SIV infection in macaques, or immunization with live, attenuated SIV and pathogenic virus challenge)."]. One or both of these specific priority areas should form the basis for the starting Research Program. The Application description of that plan should include the names of the scientists working on that project, and document their availability as well as the availability of the necessary materials. But your "Scientific Agenda" should include much more than this focused research plan; it must present your understanding of the state-ofthe-art, the key gaps in our knowledge, the obstacles to HIV/AIDS vaccine development, what you see as the opportunities for overcoming those obstacles, and a clear demonstration that you know how to turn this all into a product that can be tested in a clinical trial. You don't need to document, by letter of support, that you have available all the specific vectors and specific technical expertise (e.g. computational biologists and other experts) that you will need to implement your vision because we expect your vision to evolve. Your CV and your discussion of your HIV/AIDS vaccine accomplishments to date will list most of these experts anyway. Your CV plus, very importantly, your Strategic Plan will demonstrate to the Review Panel that you know how to find and sign on the appropriate scientific/product development/manufacturing partners. We will explain this to the Review Panel so they will not be looking for the sort of availability documentation for research

and development activities to be initiated in years 2 to 7 that they would normally expect to see in an IPCAVD application or HVDDT proposal.
As for the budget, that should be, as stated in Section 6 of the RFA, divided into three major sections (Management and Operations; Research Program; Shared Scientific Resources/Facilities). The Research Program for which you write a budget is the Director's Research Plan and the initial CHAVI research plans of the Scientific Leadership Group. The research budget will expand in years 2 to 7 as more research activities are added. Similarly, you should be able to provide detail about the Management & Operations budget and the initial Shared Scientific Resources/Facilities budget (also with expansion plans in broad outline) in your application without listing a lot of potential collaborators. We will expand on how to write the budget sections in the answer to a separate question to be posted soon on this web site.

QUESTION 2: Does the funding for the first year include indirect costs for the institution or will the indirects be added?
ANSWER: The $15 million figure is total costs; it includes indirect costs.

QUESTION 3: My research is focused on modified envelope constructs that should have the potential to induce broadly cross-reactive neutralizing antibodies. I notice that one of the Global HIV Vaccine Enterprise "Scientific Priorities" listed (3.1.iii) is to "Launch a large-scale, multiapproach attack on the neutralizing antibody (Nab) problem." However, in the CHAVI RFA you ask for the Director's Research Program to focus on one (or both) of two other of the Enterprise scientific priorities (3.1.i "vaccine design based on the characteristics of viruses causing early infection" or 3.1.ii "identify potential immune correlates of protection against SIV in selected monkey model systems"). Does this mean that the CHAVI is not supposed to tackle the neutralizing antibody problem? Another investigator I know believes that the immune response to HIV facilitates establishment of infection and thus the task should be to induce tolerance to viral antigens. Is her/his approach also outside the bounds of the CHAVI? Basically my question is whether NIAID has a list of acceptable and unacceptable vaccine development approaches for the CHAVI to pursue.
ANSWER: While the initial research of CHAVI should focus on one (or both) of the Enterprise priorities listed in the RFA, additional research activities should be described in the application's Scientific Agenda - based on the applicant's vision of the obstacles/opportunities in HIV/AIDS vaccine development. New vaccine product development should then build on the scientific results generated by the research. NIAID has no list of acceptable/unacceptable HIV/AIDS vaccine approaches; indeed NIAID hopes that different approaches will be submitted to challenge our thinking about HIV/AIDS vaccine development. The two approaches listed in your question are both acceptable IF AND ONLY IF THEY ARE DIRECTED TO RESEARCH AND DEVELOPMENT QUESTIONS OUTLINED IN THIS RFA. FOR EXAMPLE, APPROACHES THAT GIVE PERSISTENT MUCOSAL ANTIBODIES WITH BROAD NEUTRALIZATION ACTIVITY WOULD BE CONSIDERED RESPONSIVE WHILE RESEARCH ON JUST ELICITING MORE BROADLY NEUTRALIZING ANTIBODIES WITHOUT THE MUCOSAL FOCUS OR A PERSISTENCE FOCUS WOULD NOT BE. The strength, merit and coherence of the applicant's Scientific Agenda and Strategic Plan for its implementation will be evaluated by a peer review panel tasked with assessing the application's (and applicant's) potential to develop critical new knowledge about HIV immunology that will advance HIV/AIDS vaccine development. However, that said, the caveat is that you must convince the review panel of the scientific value of your position.

QUESTION 4: In the use of animal models, are models of vaccine induction that results in non-sterilizing immunity appropriate? These would be models like the SHIV 89.6 model, looking at immune correlates, and the Harriet Robinson and John Shiver models of vaccine induced protection from disease progression.
ANSWER: If you are asking whether these models fulfill the the Enterprise priority for studying the correlates of protection in nonhuman primate models then the answer is definitely "No." In order to advance the development of a prophylactic HIV vaccine the Global HIV Vaccine Enterprise has identified as a scientific priority the identification of potential immune correlates of protection in those animal models where significant protection against the

acquisition of established infection has been observed. Vaccines that allow establishment of infection with better control of viral load are important areas of research but are not the goal of this effort; these sorts of studies and vaccine constructs are being supported by other NIAID programs. However, if you have a way of using/modifying the vaccines used in the above mentioned models to induce persistent systemic and/or mucosal immunity then these models can be studied in the category of performing such research, as long as your CHAVI application also plans research on one or both of the Enterprise priority areas.

QUESTION 5: Are studies of humans infected with HIV (with antibodies and in some but not all cases CTL) who are able to maintain virtually undetectable viral loads (below 50 copies) in the absence of HAART part of the scope of work envisioned?

ANSWER: A qualified yes. If the plan is to search in early infection for a correlate of this "protection" that may extend into vaccine design or even just to describe how widespread this phenomenon may be in a developing country that could be the setting for an eventual efficacy trial then it is within in the scope of the CHAVI RFA as it is the investigation of early immunologic and virologic events after HIV-1 infection. However, if you plan to study a population here in the US and/or one that has been infected for a long time (long term non-progressors) this is not within the scope of the CHAVI RFA. CLARIFICATION: "Acute/Early infection" is defined as 0-12 months following infection. LONG-TERM FOLLOWUP OFF COHORTS IN WHICH DATA FROM THE ACUTE STAGE IS NOT AVAILABLE WILL NOT BE SUPPORTED.

QUESTION 6: To what extent is the focus of this project expected to be international?

ANSWER: This is an international pandemic and while the PI must be based in a domestic institution, the scope of vaccine discovery and certainly the clinical trials must occur in populations most affected by the epidemic so that the final product of CHAVI is indeed a vaccine where it is most needed. Thus international collaborations are encouraged, especially if you plan to focus initial research on the Enterprise priority of "elucidation of early immunologic and virologic events after HIV-1 infection in humans, including studies of exposed, uninfected persons and of HIV-infected persons during the acute to early stage of disease, with a focus on collaborating with HIV vaccine trial sites in resource-poor settings."

QUESTION 7: To what extent will the track record of the PI in leading collaborative efforts related to immunology or vaccines influence the decisions?

ANSWER: The CHAVI will have several different, although related, tasks: vaccine discovery (based on solid immunology and virology research), vaccine design, vaccine product development, and early phase clinical trials. Obviously a PI cannot be a leader in all these areas (the Scientific Leadership Group should complement the PIs expertise), but as we're really trying to address the immunological roadblocks to the discovery of a vaccine, expertise and leadership in immunology is crucial. The quality of the PI with respect to research accomplishments (track record), vision and leadership capability (in leading collaborative efforts) will be a critical factor evaluated by Peer Review. In some senses you could view this RFA as being as much about identifying a strong CHAVI director as about the specific proposed research.

QUESTION 8: Is the project intended specifically for someone who has been active in testing vaccines in the past, or is it appropriate for someone who has been doing HIV immunology?

ANSWER: We are looking for dynamic leadership, total commitment to the mission and a passion to make and deliver an HIV vaccine. Even if you have only been focused on basic HIV immunology up to now, with little or no involvement in vaccine development, you could still be a good candidate for CHAVI director. But be prepared to learn a lot about vaccine product development, GMP manufacturing and regulatory compliance, and you would be well advised to include someone with vaccine development experience in your Scientific Leadership Group.

Question 9: Can I apply to be the CHAVI Director on my own application and also be in the Scientific Leadership Group on someone else's application? Similarly, could I be named in the Scientific Leadership Group on more than one application?
Answer: For an application in response to this RFA what you propose is completely permissible.

Question 10: Since the PI will list the people in his/her own lab and long-time collaborators as personnel (salaries) can the Scientific Leadership Group do the same?
Answer: ONLY personnel essential to performing the work plan of the first year may be named in the Director and SLG research plans. DO NOT name personnel or potential collaborators that will be phased into the work of the Center after the first year.

Question 11: Can the names of subcontract animal facilities that we plan on using (especially for nonhuman primate studies) be listed?
Answer: Yes, IF SUCH WORK IS PROPOSED FOR YEAR ONE OF THE AWARD.

Question 12: Can a current employee of the VRC be the PI on a CHAVI application?
Answer: It is allowed for a current full-time employee of the VRC (or elsewhere at the NIH) to be the PI (or Director) on a CHAVI application. However, that individual must have arranged a position at an external institution to move to upon award, and the application must come through the Grants and Administration office of that institution. And the NIH employee must terminate their employment with the NIH before the award can be made. The commitment of the applicant institution as well as the ability of the PI to move to a new institution, re-establish a major research program, and devote greater than 50% of her/his effort to CHAVI research and management in the first year will be evaluated by Review.

Questions 13: Is it acceptable to have as one of the Scientific Leadership Group (SLG) someone who is currently an employee of the existing VRC?
Answer: This is allowed. However, please note that NIH policy is that while NIH intramural scientists (IMS) may participate as a member researcher of a research program funded by an extramural NIH award (like the CHAVI) they may not receive salary, equipment, supplies, or any other remuneration from the award. Furthermore the IMS must obtain written approval of the Institute's Scientific Director for allocation of intramural resources to the project(s). The letter of approval must specify a cap on the employee's % effort and a dollar cap on the direct costs of intramural resources to be allocated to the project. The expectation is that the Scientific Leadership Group will fully integrate their own work into the work of CHAVI; however, NIH policy essentially dictates that any IMS working for CHAVI will be an "unpaid consultant." Review may question the workability of such a relationship; furthermore Review may question whether either the %effort devoted to the VRC will interfere with the PI or SLG member committing full effort to CHAVI, or whether a full commitment to CHAVI may compromise the work done for the VRC

Question 14: Can a current employee of the VRC with a joint appointment at another institution be the PI or in the Scientific Leadership Group of a CHAVI application?
Answer: This is also allowed, but with the same restrictions that apply to a full time IMS applying to be either the PI or in the Scientific Leadership Group. Please note that some individuals that you may see as part time VRC members/employees are not part time federal employees but rather considered to be employees of their external institution performing work for the VRC through an Intergovernmental Personnel Act (IPA) under which they are allowed to retain extramural grants and even continue to apply for extramural support (such an IPA has a 2 year limit and can be renewed but can't exceed 4 consecutive years). The legal relationship of the applicant to the VRC should be presented clearly in the application.
Question 15: Please clarify what would be an acceptable way to have industry representatives involved in the CHAVI application. Specifically, is it acceptable to have an industry scientist that has led teams to produce GMP HIV vaccine candidates and has both experience and a company regulatory team in place as a member of the scientific leadership group?
ANSWER: It is acceptable for an applicant to include an industry person in the Scientific Leadership Group.

Question 16: If that scenario is acceptable, how would it need to be presented to indicate that because this company employee scientist was on the SLG it did not indicate that all CHAVI products would be licensed to that company?

ANSWER: Applicants are free to provide information concerning any SLG member's company/institution's IP position viz. CHAVI products. For example, the applicant may elect to include a plan detailing (1) the approach agreed to by all parties for obtaining patent coverage and licensing, where appropriate, (2) a statement demonstrating acceptance of the approach signed by all parties, and (3) the procedure to be followed for the resolution of legal problems that may potentially develop.

Question 17: If it is not acceptable to have an industry scientist on the CHAVI SLG, then what is an acceptable way to demonstrate that the applicant has an acceptable plan in place for dealing with the myriad of regulatory and production issues related to vaccine product development?

ANSWER: It is acceptable to include an industry scientist on the Scientific Leadership Group. However, there are other ways that the essential expertise related to the industry component could be demonstrated (e.g. in the Scientific Agenda and Strategic Plan; through CV's, past collaborations, university facilities, consultants, etc.). The application, as a whole, should convince the reviewers that the applicant is knowledgeable in the area of product development and that the CHAVI effort will include integral coordination and communication with experts in product development/regulatory compliance.

Question 18: For the PI's write up, do you want it to focus on early transmission or correlates of protection only kinds of studies, and does it need to be as focused as an RO1? Or do you want one specific aim on early transmission, one aim on evaluation of protection in the Lifson monkey model of ARV treatment after challenge, and one aim on adjuvants, and one aim on overcoming the need for persistent immunity re vectors (for example)? If the former, then where should the other topics to be worked on in year 1 be covered? (In the SLG write ups?) Regarding how the "PI's project on either correlates of immunity, primary HIV infection, etc." can be written, can members of the SLG contribute to this project as collaborators ?

ANSWER: The PI's research plan should be written as an R01 application with specific aims appropriate to the research plan. In some cases the PI's research plan may focus on one (or both) of the two required initial CHAVI research areas (a. early immunologic and virologic events after HIV-1 infection in humans, or b. immune correlates for protection in animal models), and this work will then be described in detail in the Director's research plan. However, in other cases the PI may not be an expert in one of these areas and chooses to focus her/his research on the other main focus of CHAVI (the systematic design and evaluation of immunogens and adjuvants eliciting persistent mucosal and/or systemic immune responses). In this case the Director's research plan must detail the work the PI (Director) plans to perform, while all other research within CHAVI should be described in the smaller sections describing the SLG members' research. SLG members may also integrate part or all of their CHAVI research with the Director's research plan, as collaborators.

Question 19: For the cores in the CHAVI application, do the core leaders have to be the members of the SLG or can they be others? If others can they be from institutions other than those of the PI and SLG or must they be from the SLG/PI institution(s)?

Regarding collaborators, if members of your team have been working with folks for years and published with them, can these collaborators be mentioned in the application?

ANSWER: Scientific core leaders do not need to be members of the SLG, and they need not be at the institutions of the PI or SLG members.

Key personnel critical to the work for CHAVI in the first year research plan(s) should be named. Those who will begin participating in the work of the Center after the first year should not be named.

Question 20: How detailed does the write up of the "product development/regulatory affairs" component of the CHAVI application need to be?

Does it need to describe in detail the entire process from preclinical studies to Phase 1 trial, and outline the individual steps from preclinical through IND? Or does it need to identify this (e.g. an office of product development and regulatory affairs) as a need to be developed and set up in year 1?

ANSWER: There must be enough information in the application for the review panel to determine that the applicant understands and is prepared to do what is required to take a vaccine design from the laboratory, get it manufactured as a product and comply with the regulatory requirements to get it into human trials.

Question 21: Is there a limit to the number of cores proposed for year 1? If there is a 10 page limit per core and a total of 50 pages for all cores, that implies that one can have 5 cores at 10 pages each or 10 cores at 5 pages each. Is that correct?

ANSWER: The page limits mean up to 5 cores in year 1. Selection of the initial cores will be an indicator of the planning and integration of the Strategic Plan and the Scientific Agenda. The plans and process for addition or expansion of Shared Resources (shared cores) in future years will also count in the evaluation of the integration of the Strategic Plan, the Scientific Agenda, and Management and Operations/project management.

Question 22: Is training of young investigators and new faculty an important mission of CHAVI? Can CHAVI have a new faculty development program, whereby new faculty are hired to work on an HIV/AIDS vaccine?

ANSWER: No; training of new investigators is not a stated goal of the CHAVI. The goal of CHAVI is to get a vaccine. If the sponsoring institution sees the presence of a CHAVI at their institution as a unique opportunity to train new investigators and chooses to take advantage of this large center at their site, a separately funded training program could be coordinated with the efforts of CHAVI. The joint focus on HIV and immunology may provide a nexus for institutions to develop a new focus to their training/mentoring programs. Salaries of any employee (which could include graduate students and postdoctoral fellows, depending on sponsoring institution requirements for the status as "employee") working on CHAVI research activities can be supported by the CHAVI award in the same way as on other NIH research grant awards.

Question 23: How should we handle writing the budgets for years 2-7? Is the total award $350M?

ANSWER: The current estimated funding levels are: up to $14.9 million for the first year, with future year anticipated levels of up to $49 million per year for budget periods 02 though -07. Based on this information, the total seven year project period will not exceed $308.9 million, and could be less.

Future year budgets will understandably be estimates or projections only. However, these estimates should be based on your experience and plans for future CHAVI activities. Budget requests should reflect the level and the types of costs necessary to meet the long term objectives.

Please use the multi-project budget chart to present the overall/composite budget in lieu of the PHS 398 form page 4. You may download this Summary Budget Chart from the NIAID/DEA website, http://www.niaid.nih.gov/ncn/grants/multi/5a.htm

With respect to the CHAVI director's initial research project, Research Program Section, a detailed budget similar to a regular R01 or P01 project should be provided, utilizing the PHS 398 form pages.